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Exploiting the CNC Side Chain in Heterocyclic Rearrangements: Synthesis of 4(5)-Acylamino-imidazoles

Antonio Palumbo Piccionello,* Silvestre Buscemi, Nicolò Vivona, and Andrea Pace

Dipartimento di Chimica Organica "E. Paternò", Università degli Studi di Palermo, Viale delle Scienze-Parco d'Orleans II, I-90128 Palermo, Italy

apalumbo@unipa.it

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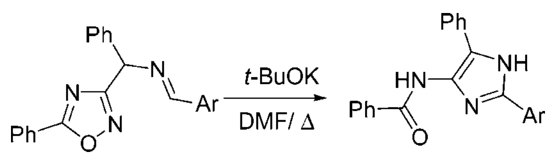
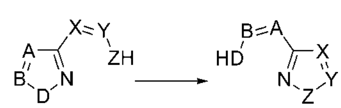
ABSTRACT



A new variation on the Boulton−Katritzky reaction is reported, namely, involving use of a CNC side chain. A novel Montmorillonite-K10 catalyzed nonreductive transamination of a 3-benzoyl-1,2,4-oxadiazole afforded a 3-(α-aminobenzyl)-1,2,4-oxadiazole, which was condensed with benzaldehydes to afford the corresponding imines. In the presence of strong base, these imines underwent Boulton−Katritzky-type rearrangement to afford novel 4(5)-acylaminoimidazoles.

The Boulton−Katritzky (BK) rearrangement represents one of the most investigated ring-transformation reactions[1] as a result of its synthetic applications[2,3] and intriguing mechanistic aspects.[4,5]

It consists of an interconversion between two five-membered heterocycles where a three-atom side chain and a pivotal annular nitrogen are involved (**1** → **2**).[1] This rearrangement typically occurs on O−N bond-containing heterocycles (D = O)[3,6] with the O(1) ring oxygen acting as an internal leaving group. The O−N bond is cleaved by the nucleophilic attack of the side-chain Z atom at the electrophilic N(2) ring nitrogen. This reaction is affected by the aromaticity and relative stability of the five-membered heterocycles **1**and **2**. Moreover, with Z atoms different from oxygen, the reaction is irreversibly shifted toward the formation of a more stable N−N, S−N, or C−N bond.



1 **2**

Although the effect of the type of side chain (X = Y−ZH) on the obtainment of different heterocycles has been extensively investigated,[3b] few studies have regarded the involvement of a nucleophilic carbon (Z = C) at the side chain. The only examples of this kind have involved a NCC side chain in the base-induced rearrangement of *N*-(1,2,4-oxadiazol-3-yl)-*β*-enaminoketones into imidazoles[7,8] and involved a NNC side chain recently reported for the thermal rearrangement of *N*-(1,2,4-oxadiazol-3-yl)hydrazones into 1,2,4-triazoles.[9] Therefore, in the context of our research on heterocyclic rearrangements, we wanted to investigate the

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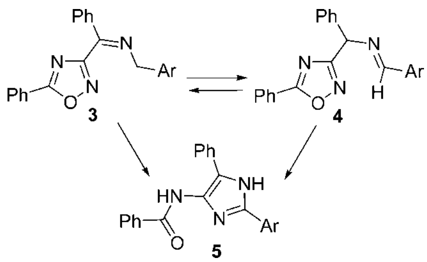
occurrence of a BK rearrangement of tautomeric imines **3** and **4**, which contain a CNC side chain linked to the C(3) of a 1,2,4-oxadiazole ring, into imidazole derivatives **5** (Scheme 1).

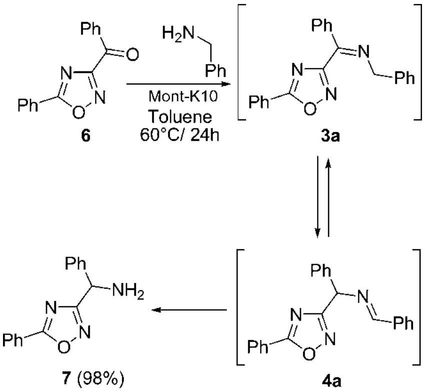
Scheme 1. CNC Side-Chain Rearrangement of 1,2,4-Oxadiazole



Any attempt to obtain imines **3** directly from oxadiazole **6**[10] through classic methods failed because of product hydrolysis during the workup of the reaction mixture. On the other hand, isolation of amine **7** in almost quantitative yield was achieved by reaction of **6** with benzylamine in toluene at 60 °C for 24 h and in the presence of Montmorillonite K10 (Mont-K10) (Scheme 2). Formation of amine **7** is explained on the basis of a nonreductive transamination of ketone **6** with benzylamine acting as nitrogen donor. According to Montmorillonite-promoted imine formation,[8,11] this pathway consists of an initial Mont-K10-catalyzed condensation of benzylamine with ketone **6**.

Nevertheless, the acid catalyst will also promote tautomerization of **3a** into imine **4a** and the final hydrolysis into amine **7** (Scheme 2). This reaction represents the first example of a biomimetic nonreductive transamination involving the employment of an acidic heterogeneous catalyst and exploiting a one-pot methodology.

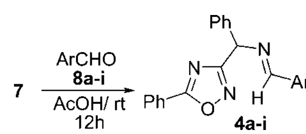
Scheme 2. Preparation of Amine **7**



In fact, the nonreductive transamination of ketones usually occurs with base-catalyzed 1,3-proton shift of imines and subsequent hydrolysis,[12] although acidic[13] or thermally induced[14] tautomerization of fluorinated imine-derivatives have been recently proposed.

The amine **7** was then used for the synthesis of imines **4a−i** through condensation with aromatic aldehydes **8a−i** (see Table 1).

Table 1. Condensation of Amine **7** with Aldehydes **8a−i**



entry	product	**4** yield (%)[a]
1	**a**: Ar = Ph	97
2	**b**: Ar = 4-MePh	89
3	**c**: Ar = 4-MeOPh	95
4	**d**: Ar = 4-NO_2Ph	91
5	**e**: Ar = 4-CF_3Ph	82
6	**f**: Ar = 4-FPh	85
7	**g**: Ar = 4-ClPh	88
8	**h**: Ar = 4-BrPh	80
9	**i**: Ar = 4-Me_2NPh	83

[a] Isolated yields.

The reactions were conducted at room temperature by using acetic acid as solvent, and the final products were obtained in pure form by crystallization of the reaction residue (see Supporting Information). The latter approach

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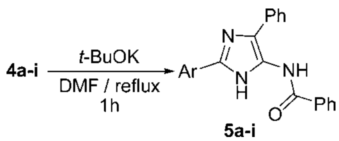
(14) Yasumoto, M.; Ueki, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2007**, *128*, 736–739.

represented a significant improvement in terms of workup procedures by avoiding chromatographic purification and consequent hydrolysis of the imino moiety and allowing high yields of the final product to be isolated. The classic X = Y−ZH sequence in the general BK rearrangement scheme (see above) points out the key role of the potentially acidic Z−H proton.

Table 2. Rearrangement of Imines **4** into Imidazoles **5**

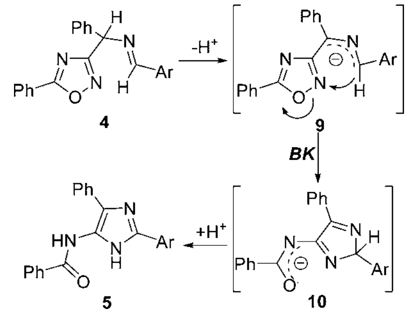


entry	product	**5** yield (%)[a]
1	**a**: Ar = Ph	89
2	**b**: Ar = 4-MePh	86
3	**c**: Ar = 4-MeOPh	63
4	**d**: Ar = 4-NO_2Ph	80
5	**e**: Ar = 4-CF_3Ph	80
6	**f**: Ar = 4-FPh	76
7	**g**: Ar = 4-ClPh	71
8	**h**: Ar = 4-BrPh	71
9	**i**: Ar = 4-Me_2NPh	52

[a] Isolated yields.

Deprotonation under basic conditions generates the X = Y−Z^- anionic side chain where Z^- is the nucleophilic site attacking the N(2). In substrates **4a−i**, such deprotonated side chain can be achieved considering the potential acidic character of methine C−H directly linked to C(3) of the oxadiazole ring. In fact, thermal rearrangement reactions of **4a−i** under basic conditions (*t*-BuOK) in refluxing DMF yielded imidazoles **5a−i** in good to high yields (Table 2). On the other hand, attempts to perform this rearrangement in the absence of a base by refluxing compounds **4** in most common organic solvents (toluene, benzene, DMF, acetonitrile) or by heating under solvent-free conditions, led to decomposition of starting material. Moreover, the use of protic solvents (MeOH, EtOH) led to hydrolysis of the imines **4a−i** into amine **7** and the corresponding aldehyde **8a−i**. These findings confirmed the requirement of a base for the reaction to occur. From a mechanistic point of view, the driving force of the reaction could be ascribed to the higher aromatic stabilization of the imidazole ring with respect to the 1,2,4-oxadiazole, according to Bird's index.[15] According to the general scheme of the BK rearrangement, the involvement of the base in the formation of imidazoles **5** is explained through the initial formation of allyl anions **9**, which undergoes an internal nucleophilic substitution at the pivotal N(2) atom of the oxadiazole ring. Rearomatization of intermediates **10** and final protonation produces target imidazoles **5** (Scheme 3). In conclusion, we report the first example of a CNC side chain involved in the Boulton−Katritzky reaction, which enhances the breadth of this well-studied and widely applied reaction. Starting substrates were obtained through an unprecedented Mont-K10-catalyzed nonreductive ketone transamination, whose general applicability is currently under investigation.

Scheme 3. Proposed Mechanism for BK Rearrangement of Compounds **4**



Considering the biological activity of 4(5)-acylamino-imidazoles[16] and the renewed interest in the synthesis of 4(5)-aminoimidazoles,[17] the reported rearrangement represents a valid approach toward target imidazoles. The precursor accessibility, the easy workup, and the good product yields, encourage further use of this synthetic methodology.

Acknowledgment. Financial support through the University of Palermo is gratefully acknowledged.

Supporting Information Available: Synthetic details, characterization data, and ^{1}H and ^{13}C NMR spectra of compounds **4**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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